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DAFFER MCDANIEL LLP
P.O. BOX 684908
AUSTIN, TX 78768

EXAMINER	
CLOW, LORI A	
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MARK CHANDLER and VAN S. CHANDLER

Appeal 2008-2658
Application 09/662,790
Technology Center 1600

Decided: July 15, 2008

Before TONI R. SCHEINER, DEMETRA J. MILLS, and
LORA M. GREEN, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1-7, 40, and 41.[1] We have jurisdiction under 35 U.S.C. § 6(b). Claims 1, 3, and 4 are representative of the claims on appeal, and read as follows:

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[1] Claim 39 is also pending, but stands withdrawn from consideration (App. Br. 2).

1. A Multi-Analyte Profile (MAP) Test Panel comprising 75 or more subsets of microspheres, wherein the microspheres of one subset are distinguishable from those of another subset by their characteristic fluorescence signatures, and wherein the microspheres of the one subset are coupled to at least one reagent designed to interact selectively with a predetermined analyte.

3. The MAP Test Panel of claim 1, wherein the characteristic fluorescence signatures are derived from at least three fluorescent dyes incorporated in the microspheres.

4. The MAP Test Panel of claim 1, wherein the characteristic fluorescence signatures are derived from at least four fluorescent dyes incorporated in the microspheres.

The Examiner relies on the following references:

J.R. Kettman et al., "Classification and Properties of 64 Multiplexed Microsphere Sets," 33 *Cytometry*, 234-243 (1998).

Ekins, "Multi-analyte immunoassay," 7(2) *Journal of Pharmaceutical & Biomedical Analysis*, 155-168 (1989).

We affirm.

BACKGROUND

According to the Specification, the "invention relates to the creation and use of a database comprising biochemical data for a wide range of applications, including diagnosis of disease states, the prognosis for recovery, determination of the onset (or potential thereof) of future disease states, assessment of health or medical conditions or the like." (Spec. 1).

As to the claimed subsets of microspheres, the Specification teaches:

> Consistent with the objectives of the present invention, a Multi-Analyte Profile (MAP) Test Panel is also provided, which comprises 20 or more subsets of microspheres, the

> microspheres of one subset being distinguishable from those of another subset and harboring at least one reagent designed to interact selectively, if not specifically, with a predetermined analyte. In preferred embodiments of the invention the MAP Test Panel comprises 50 or more, 75 or more, 100 or more, 200 or more, or 300 or more subsets of microspheres. In a specific embodiment of the invention, the microspheres of one subset are distinguishable from those of another subset by their characteristic fluorescence signatures. Elsewhere in this specification, microspheres having this characteristic fluorescence signature might also be referred to as fluorescence addressable microspheres. The microspheres of the MAP Test Panel typically contain various concentrations of at least two or more fluorescent dyes, sometimes at least three or more fluorescent dyes and, preferably, at least four or more. The at least one reagent comprises any substance that can selectively, if not specifically, interact with an analyte of interest. Typically, the reagent comprises a small molecule, natural product, synthetic polymer, peptide, polypeptide, polysaccharide, lipid, nucleic acid, or combinations thereof. The predetermined analyte can be any of a wide range of substances also. Typically, the predetermined analyte comprises a drug, hormone, antigen, antibody, protein, enzyme, DNA, RNA, or combinations thereof.
>
> Accordingly, the present invention also provides a kit for assaying 20 or more predetermined analytes in a single pass through a flow analyzer comprising a Multi-Analyte Profile (MAP) Test Panel comprising 20 or more subsets of microspheres, the microspheres of one subset being distinguishable from those of another subset and harboring at least one reagent designed to interact selectively, if not specifically, with a predetermined analyte.

(Spec. 3-4.) The Specification teaches further that "[e]ach of the twenty or more reagents is coupled to a specific subset of microspheres, which are dyed with two types of fluorescent materials, such that each subset exhibits a characteristic fluorescence signature," and is "prepared, each according to

methods similar to those described, e.g., in PCT Application Number US98/21562." (*Id.* at 20.)

DISCUSSION

Claims 1-7, 40, and 41 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Kettman and Elkins.

Kettman is cited for teaching "a method and system for analysis of multiple analytes in a single sample." (Ans. 5.) Kettman is also cited for teaching a system for analyzing 64 analytes, the vehicle for which consists of a set of microspheres identifiable by characteristic fluorophores embedded in the particles (*id.* at 6). According to the Examiner, Kettman teaches that in the 64 microsphere system, two fluorescent dyes, a red and an orange, are embedded in the microsphere, and a target molecule is attached to the microsphere, and the reporter molecule that binds to the microsphere is labeled with a green fluorphore (*id.*). Kettman is also cited for teaching that the "panels are useful for analysis of antibodies, antigens, and other soluble molecu;es, including nucleic acids, drugs, and enzymes." (*Id.*)

The Examiner notes that Kettman does not specifically teach more than 64 subsets of microspheres (Ans. 6). The Examiner thus relies on Ekins for teaching multi-analyte immunoassays "in which tens or hundreds of substances can be measured simultaneously," which the Examiner notes suggests "increasing the analyte and microsphere values in order to increase the capability of medical diagnosis and drug design, for example." (*Id.*) The Examiner concludes:

> It would have been prima facie obvious to one of ordinary skill in the art at the time if invention to have incorporated more than 75 analytes/microspheres into the invention of Kettman [ ] as

> suggested by Ekins. One would be motivated to do so by the teachings of Ekins, which state that "fluorescent labels are particularly useful in this context because they readily permit arrays of different antibody "microspots" distributed over a surface, each directed against a different analyte, to be individually examined, thus enabling multiple assays to be simultaneously carried out on the same small sample. The same principals are clearly applicable using other forms of label (page 166, lines 16-2 1)". One of ordinary skill in the art would have reasonably expected success in using hundreds of microspheres because Ekins teaches, "it is both conceivable and within the range of present technology that immunoprobes will be developed capable of measuring every hormone (or isohormone component), together with other endocrinologically related substance within a single small sample of blood, providing data which, when analyzed with the aid of computer based "expert" pattern recognition systems, will reveal endocrine deficiencies only dimly perceived using current "single analyte" diagnostic procedures (page 167, lines 12-19)".

(*Id.* at 6-7.)

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The Supreme Court has recently emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). "The combination of familiar elements according to known methods is likely to be obvious when

it does no more than yield predictable results." *Id.* at 1739. Moreover, an "[e]xpress suggestion to substitute one equivalent for another need not be present to render such substitution obvious." *In re Fout*, 675 F.2d 297, 301 (CCPA 1982).

Appellants argue that there "is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to combine Kettman and Ekins as suggested." (App. Br.[2] 6.) Kettman, Appellants assert, only discloses an assay using 64 mutiplexed microsphere sets, that the number of microsphere sets is limited by the uniformity of the microspheres, and that the number of microsphere sets is limited by the fluorescence uniformity among the microsphere members of each set (*id.* at 6-7).

Appellants argue further that "Kettman teaches that variations in the microspheres themselves and the dye content within the microspheres affect the fluorescence used to determined the set to which a microsphere belongs," thus teaching "that the number of microsphere sets that can be included in an assay is limited at least in part by the variations in the microspheres themselves and the dye content within the microspheres." (App. Br. 7.) That may be, Appellants contend, why Kettman teaches that the system can analyze up to 64 analytes (*id.*). Ekins, Appellants assert, is drawn to a multi-analyte immunoassay that utilizes antibody molecules attached to a solid support, and the fluorescent markers are external to the sold substrate (*id.* at 8). Thus, Appellants assert, Kettman and Elkins "rely on completely different technologies to create an assay." (*Id.*)

[2] All references to the Appeal Brief are to the Supplemental Appeal Brief dated May 30, 2007.

Appellants also argues that the prior art teaches away from the combination, as Kettman teaches away from attaching fluorescent-based labels to the surface (App. Br. 9-10). Ekins, Appellants assert further, "does not teach any 'sets' that can be used in analyte analysis," and thus "cannot teach or suggest that more than 64 sets can be used in analyte analysis with a reasonable expectation of success." (*Id.* at 10.) According to Appellants, as "Ekins teaches that analyzing tens or hundreds of analytes is feasible using a technology different than the technology taught by Kettman, Ekins does not teach or suggest that using more than 64 microsphere sets for analyte analysis is technically feasible." (*Id.* at 12.)

As to motivation to combine, the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1739 (2007), rejected a rigid application of the teaching-suggestion-motivation test. The Court recognized that it is often necessary to look at the interrelated teaches of multiple references; the effects of demands of the marketplace; and the background knowledge possessed by a person of ordinary skill, "all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed." *Id.* at 1740-41. Moreover, the "obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, or motivation, or by overemphasis on the importance of published articles and explicit content of issued patents." *Id.* at 1741. Finally, one "of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of the invention a known problem for which there was an obvious solution encompassed by the patent's claims." *Id.* at 1742.

In this case, Kettman teaches a method for the analysis of multiple analytes, the vehicle for which is a set of microspheres identifiable by

characteristic fluorophores in the particles (Kettman, Abstract). Two dyes, whose proprietary properties were not described, were used in the formation of the particles, one dye providing red fluorescence and one dye providing orange fluorescence (Kettman, p. 235, second column). In addition, Kettman uses a green fluorophore to determine interaction at the surface of the microsphere (Kettman, p. 241, first column). The microspheres of Kettman are measured by flow cytometry using the FlowMetrix system (Kettman, p. 234, second column). As to the design of the microspheres, Kettman teaches:

> Several observations have been made regarding the use of dyes dissolved in the microspheres. Because the dyes are inside the microspheres, solvent conditions will not affect the dye characteristics. . . . Although the microsphere population is reasonably uniform, small differences in size and or composition alter the relative dying efficiency. Additionally, as the dye content is increased, the spectrum of the combination of two dyes changes.
>
> Because the efficiencies of each dye are very different when stimulated with 488-nm light, to achieve usable signal levels, different concentrations of each dye must be used. The molarity of the orange-emitting dye is lower than that of the red-emitting dye. This difference has practical consequences when applied to fluorescence energy transfer (FRET). Each fluorophore must have overlapping emission and absorption spectra and must be within a certain distance for FRET to be effective (<60 angstroms). FRET can occur in microspheres (commercial products depend on this feature for their microsphere absorption and emission characteristics). By keeping at least one of the dyes at a lower molarity than the other, FRET can be kept to a minimum.

(Kettman, p. 241, col. 1.)

Therefore, Kettman teaches a Multi-Analyte Profile (MAP) Test Panel comprising *64* subsets of microspheres, wherein the microspheres of one subset are distinguishable from those of another subset by their characteristic fluorescence signatures, and wherein the microspheres of the one subset are coupled to at least one reagent designed to interact selectively with a predetermined analyte. Kettman thus teaches all of the limitation of claim 1 except for teaching that the MAP test panel comprises *75* or more subsets of microspheres.

Ekins teaches the reasons why the ordinary artisan would want to measure 75 or more analytes simultaneously, by teaching that "measuring tens or hundreds of analytes, or molecular variants of the same functionally defined substance, in the same sample is . . . of great importance." (Ekins, p. 165.) Therefore, Ekins was cited merely for its teaching of why the ordinary artisan would want to adapt the system of Kettman to include more than 64 subsets of microparticles, such as providing 75 or more such subsets.

We recognize that Kettman only specifically teaches the use of two proprietary fluorophores to generate the set of 64 microspheres. But the ordinary artisan would understand that additional sets can be generated using a different pair of dyes, or by adding a third or fourth dye.[3] Kettman is

[3] We note that Appellants' Specification supports our finding that it would have been well within the level of ordinary skill to select different pairs of dyes, or to add a third or fourth dye, to generate a subset of microspheres for the analysis of multiple analytes as taught by Kettman. Appellants' Specification does not provide any guidance as to the dyes to be used, or the methods used to generate the microspheres. A Specification, however, need not disclose what is well known in the art. *In re Buchner*, 929 F. 2d 660, 661 (Fed. Cir. 1991). Thus, the fact that the Specification is silent on the fluorophores used in the microparticles, as well as the generation of the

focused on generating a uniform set of microspheres with reproducible properties, which is why Kettman looks at microsphere size, etc., of the set. But, Kettman provides the method of generating one such set with a single fluorophore pair, but the ordinary artisan would have understood that the same considerations would be used in generating a second set based on different fluorophores or by adding a dye or two to the dyes of Kettman. As noted by the Court in *KSR*, "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton." 127 S. Ct. at 1742.

As to claims 3 and 4, claim 3 requires that the characteristic fluorescent signature be derived from at least three fluorescent dyes, and claim 4 requires that the characteristic fluorescent signature be derived from at least four fluorescent dyes (App. Br. 16). Kettman, Appellants argue, "discloses microsphere subsets that are distinguishable from other microsphere subsets by characteristic fluorescence signatures that are derived from two fluorescent dyes incorporated into the microspheres," and "Ekins does not disclose microspheres." (*Id.* at 17.) Thus, Appellants assert, neither Kettman nor Ekins, alone or in combination, teach the limitations of claims 3 and 4 (*id.*).

Appellants' arguments have been considered, but are not deemed to be persuasive for the reasons set forth with respect to claim 1. Thus, we also affirm the rejection as to claims 3 and 4.

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particles, is evidence that Appellants considered it to be within the skill level of the ordinary artisan to choose the appropriate fluorophores and produce the claimed microparticles.

CONCLUSION

In summary, we conclude that the Examiner has set forth a prima facie case of obviousness that has not been adequately rebutted by Appellants, and the rejection is affirmed.

No time period taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

Ssc:

DAFFER McDANIEL LLP
P.O. BOX 684908
AUSTIN, TX 78768